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(21) International Application Number: PCT/SE99/00426 (22) International Filing Date: 18 March 1999 (18.03.99) (30) Priority Data: 9801368-3 20 April 1998 (20.04.98) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): PERSSON, Carl, Göran [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE). BRATTSAND, Ralph [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE). OHLSSON, Stefan [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: USE OF A GLUCOCORTICOSTEROID FOR THE MANUFACTURE OF A MEDICAMENT FOR TREATING MILD/EARLY FORMS OF COPD (CHRONIC OBSTRUCTIVE PULMONARY DISEASE) (57) Abstract The invention relates to the use of a glucocorticosteroid for the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD) in patients having an FEV _{1.0} value > 65 % of predicted value and < 10 % reversibility in bronchodilator test. The invention further relates to a method for treatment of COPD in patients having an FEV _{1.0} value > 65 % of predicted value and < 10 % reversibility in bronchodilator test, where a therapeutically effective amount of a glucocorticosteroid is administered to a patient in need of such treatment.		

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USE OF A GLUCOCORTICOSTEROID FOR THE MANUFACTURE OF A MEDICAMENT FOR TREATING MILD/EARLY FORMS OF COPD (CHRONIC OBSTRUCTIVE PULMONARY DISEASE)

FIELD OF THE INVENTION

5 The present invention relates to the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease (COPD). More particularly the invention relates to the use of a glucocorticosteroid for treating mild/early form of COPD.

BACKGROUND OF THE INVENTION

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Chronic obstructive pulmonary disease (COPD) is a common disease in industrialized countries (about 6 % of the men and 4 % of the women over 45 years in the UK are affected) and responsible for a considerable morbidity and mortality. Most of the patients are smokers. The two most important conditions associated with COPD are chronic bron-

15 chitis and emphysema.

20

Chronic bronchitis is a long-standing disease of the bronchi involving increased production of mucous and other mucosal changes. The symptoms are cough and expectoration of sputum and as the disease progresses shortness of breath. Chronic bronchitis exhibits

20 exacerbations frequently due to recurrent infections. Over many years narrowing and plugging of the bronchi cause difficult breathing and eventually general disability. The annual decline in airflow resistance is normally progressive and may be accompanied by airway hyper-responsiveness. However, in contrast to asthma the hyper-responsiveness is largely dependent on the baseline obstruction and the baseline obstruction is little reversed

25 by bronchodilator treatment.

30

Emphysema is a chronic lung disease which affects the alveoli and/or the ends of the smallest bronchi. The lung loses its elasticity and areas of the lungs become destroyed with enlarged air spaces. These enlarged areas trap 'stale' air and do not effectively exchange it

30 with fresh air. This results in difficult breathing and may result in insufficient oxygen being

delivered to the blood. The predominant symptom in patients with emphysema is shortness of breath.

Treatment of COPD is often unsatisfactory. At present COPD is treated only in its more
5 developed stages using a variety of inhaled or orally administered bronchodilators or
inhaled anti-cholinergic agents. In more severe COPD orally administered steroids and
inhaled steroids, such as glucocorticosteroids, may be continued if the patients demonstrate
improvement during the first few weeks of treatment. The problem with these treatments is
that none of them has been regarded as effective. A recent review of new therapies for
10 COPD has just been published (Thorax, 53 (1998), 137-147). Here it is clearly stated that
there is scarcely no evidence that glucocorticosteroids are beneficial in COPD. Inhaled
fluticasone propionate has recently been compared with placebo in the treatment of patients
with moderate COPD for 6 months (Lancet 351 (1998), 773-780). Marginal but statistically
significant improvement was observed in some disease variables but the major aspect of
15 COPD, the progression of the disease, was not addressed in this study. To explain their
data the authors speculate that in severe COPD some degree of steroid sensitive inflammation
might contribute to the disability of this patient group.

As regards mild stages of COPD when airway obstruction is marginally to moderately
20 abnormal it is considered that anti-inflammatory therapy is without effect or the effect of
drugs such as inhaled steroids are small and transitory (Eur. Resp. J. 5 (1992), 1254-1261;
Lancet, 351 (1998), 766-767; Thorax 53 (1998), 137-147). Of greatest concern is the lack
of therapy (except smoking cessation) that can reduce the progression of the disease i.e. to
slow down the rate of annual decline in the forced expiratory volume in 1 second (FEV_{1.0}).
25 This lack of effective therapy applies to COPD patients irrespectively of the disease stage.
Cessation of smoking has been shown to decrease the rate of decline of lung function in
COPD and is, at this time, the only proven successful long-term therapeutic intervention in
COPD. However, stop smoking has proved to be very difficult for the majority of patients.
It appears particularly unfortunate that currently there is no known drug treatment that can
30 reduce the progression of the disease in patients who have only mild/early COPD, but are

at high risk of suffering rapid decline in their lung function thus taking them towards severe disability.

It is known from Renkema et al, Chest 109 (1996), 1156-1162 that corticosteroids can be
5 used in long-term treatment of patients with COPD. It is, however, clearly stated that when
assessing the effectiveness of corticosteroids in patients with COPD, it is essential to
exclude patients with asthma, i.e. to exclude patients having > 10 % reversibility in
bronchodilator test. Furthermore, it is stated that "studies performed thus far show that the
beneficial effects of long-term treatment with corticosteroids in patients with COPD are
10 small and less prominent than in patients with asthma".

Accordingly it is an object of the present invention to find suitable compounds for the
manufacture of a medicament for treatment of mild/early COPD including attenuation of
the decline in lung function.

15

It is a further object of the invention to present a method for treatment of patients suffering
from mild/early COPD.

SUMMARY OF THE INVENTION

20

According to the present invention it has surprisingly been found that glucocorticosteroids
are effective in treating mild/early COPD in spite of continuous exposure to causally-
related factors, in particular tobacco smoking e.g. cigarette smoking. Mild COPD patients
are defined as patients having a forced expiratory volume in 1 second (FEV_{1.0}) values > 65
25 % of predicted FEV_{1.0}, and they are distinguished from asthma by having < 10 % reversi-
bility in bronchodilator test.

According to the invention there is provided use of a glucocorticosteroid for the
manufacture of a medicament for treating chronic obstructive pulmonary disease in patients

having a $FEV_{1.0}$ value $> 65\%$ of predicted value and $< 10\%$ reversibility in bronchodilator test (measurements of $FEV_{1.0}$ and reversibility using a bronchodilator).

According to a further aspect of the invention a method of treatment of chronic obstructive pulmonary disease in patients having a $FEV_{1.0}$ value $> 65\%$ of predicted value and $< 10\%$ reversibility in bronchodilator test is provided. The method is characterized by administration to the patient in need of such treatment of a therapeutically effective amount of a glucocorticosteroid.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 Linear change over time for all patients.

Fig. 2 Linear change over time for patients with < 26 pack-years (as defined below). The treated patients have an annual decline in lung function that approaches that of some normal health individuals.

Fig. 3 Linear change over time for patients with < 36 pack-years (as defined below).

Fig. 4 Linear change over time for patients with > 36 pack-years (as defined below).

Fig. 5 Difference in linear change over time, by pack-year (as defined below).

DETAILED DESCRIPTION OF THE INVENTION

The successful result of the treatment of mild COPD with glucocorticosteroids has been demonstrated in the present invention by the treatment of a large group of patients during a period of three years. The patients were chosen to fulfill the criteria of mild COPD as set out above and they were all smokers.

The results of the clinical trials show that early use of a glucocorticosteroid in mild/early COPD will improve the patients situation considerably i.e. the progressive course of the disease has been significantly decreased by the treatment. The beneficial effect of the steroid treatment on annual decline in $FEV_{1.0}$ is more pronounced for people who have a

lower smoke exposure than for the heavy smokers (Figure 5). Patients having more than 36 pack-years benefit less and thus will be difficult to treat adequately although some may receive benefit from the treatment. However, based on the new data also this more severely smoke-exposed patient category may become more responsive to the treatment of the present invention if they manage to reduce their smoking. Therefore, the present invention can be used for the manufacture of a medicament for treating COPD in patients having a smoking exposure of less than 46 pack-years, suitably less 36 pack-years, preferably less than 26 pack-years and more preferably less than 16 pack-years.

As can be seen from the Figures the treatment period must be of a certain length before any effect will be distinguished. A treatment period of at least one year is necessary. Preferably the patients are treated for at least three years.

The glucocorticosteroid used in the invention is preferably an anti-inflammatory glucocorticosteroid. Among the glucocorticosteroids which can be used for the manufacture of the medicaments according to the present invention the following can be mentioned: betamethasone (e.g. as valerate), fluticasone (e.g. as propionate), budesonide, tipredane, dexamethasone, beclomethasone (e.g. as dipropionate), prednisolone fluocinolone, triamcinolone (e.g. as acetonide), mometasone (e.g. as furoate), rofleponide (e.g. as palmitate), flumethasone, flunisolide, ciclesonide, deflazacort, corticazol, 16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione, 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 α -methylthio-androsta-4-ene-3-one, S-methyl 16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β hydroxy-3-oxo-androsta-1,4-diene 17 β -carbothioate, methyl 9 α -chloro-6 α -fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 α -carboxylate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carbothioic acid S-2(2-oxo-tetrahydrofuran-3S-yl) ester, optionally in their pure isomeric forms (where such forms exist) and in the forms of their esters, acetals and salts. Preferably, use is made of budesonide, rofleponide, rofle-ponide palmitate, momethasone furoate, beclomethasone

dipropionate or fluticasone propionate, more preferably of budesonide, rofleponide or rofleponide palmitate, e.g. as the 21-palmitate, and most preferably of budesonide.

For administration, the medicament is suitably inhaled from a nebulizer, from a pressurized
5 metered dose inhaler or as a dry powder inhaler, e.g. Turbuhaler® (trademark of Astra of Sweden) or from a dry powder inhaler utilizing gelatin, plastic or other capsules, cartridges or blister packs. The administration of the medicament may be by nasal or preferably oral inhalation.

10 According to the invention the glucocorticosteroid is preferably administered in the form of either

- 1) agglomerated particles comprising particles of the steroid of the particle size of less than 10 μm ,
- 2) agglomerated particles comprising particles of the steroid and a carrier, both of which
15 have a particle size of less than 10 μm , or
- 3) an ordered mixture comprising steroid particles of a size less than 10 μm and coarser particles of a carrier, optionally also particles of the carrier of a particle size less than 10 μm . The coarser carrier particles could also be agglomerates of small particles.

20 The amount of glucocorticosteroid administered to the patient is preferably from 100 μg to 3000 μg per day, more preferably from 200 μg to 1600 μg administered as a single or divided dose/s one to four times per day. Highly preferred doses are 200 μg given twice a day or 400 μg given twice a day.

25 The glucocorticosteroids can be used in admixture with one or more pharmaceutically acceptable additives, diluents or carriers, preferably in an amount of from 100 μg to 25 mg per dose, more preferably in an amount of from 100 μg to 10 mg, most preferably in an amount of from 100 μg to 2000 μg per dose. Examples of suitable diluents or carriers include lactose, dextran, mannitol or glucose. Preferably lactose is used, especially as the
30 monohydrate.

One or more of the ingredients is preferably in the form of a dry powder, more preferably a micronized dry powder. Most preferably an agglomerated micronized dry powder is used. As an alternative to agglomeration, the finely divided glucocorticosteroid may be in the form of an ordered mixture with the pharmaceutically acceptable additive, diluent or carrier. An ordered mixture comprises fine particles of the substance in association with mainly coarse particles of the pharmaceutically acceptable additive, diluent or carrier, e.g. wherein at least about 70 % by weight, suitably at least 90 % by weight, of the coarse particles have a particle size of more than about 20 μm . The ingredients used in the invention can be obtained in these preferred forms using methods known to those of skill in the art.

When the medicament is adapted to be administered from a pressurized inhaler, it is preferably in finely divided e.g. micronized form. It may be dissolved or, preferably suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an anti-oxidant and/or stabilizing agent.

When the medicament is adapted to be administered via a nebulizer it may be in the form of a nebulized aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multi-dose device.

EXAMPLES

The invention will now be illustrated by the following Examples, which are not intended to limit the scope of the invention.

5

In the Examples micronization is carried out in a conventional manner such that the particle size range for each component is suitable for administration by inhalation.

Example 1

10 9 parts of budesonide and 91 parts of lactose monohydrate were micronized separately in a spiral jet mill at a pressure of about 6-7 bars to give a particle size of less than 3 μm before being mixed thoroughly in a Turbula mixer. Before mixing, the lactose monohydrate powder was conditioned according to the method described in US patent 5,709,884 to remove amorphous regions in their crystal structure. The mixture was remicronized in a
15 spiral jet mill at a pressure of only about 1 bar to obtain a uniform mixture. The powder was then agglomerated by feeding the powder into a twin screw feeder (K-Tron), sieving in an oscillating sieve (0.5 mm mesh size), spheronizing in a rotating pan with a peripheral speed of 0.5 m/s for 4 minutes and then sieving again using the same sieve, then spheronizing once more for 6 minutes before final sieving (mesh size 1.0 mm) to give a
20 powder of a bulk density of 0.35 g/ml.

Example 2

200 parts by weight of micronized budesonide was mixed with 800 parts of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then con-
25 ditioned using the process of US 5,709,884. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler®.

Example 3

400 parts of budesonide was micronized in an spiral jet mill, spheronized using the process
30 of EP-A-721 331 and filled into the storage compartment of Turbuhaler®.

Example 4 - Clinical Trials

A glucocorticosteroid was used for treatment of mild COPD in a large group of patients during a period of three years. The patients were chosen to fulfill the criteria of mild COPD and they were all smokers. Mild COPD patients are defined as patients having a forced expiratory volume in 1 second (FEV_{1.0}) values > 65 % of predicted FEV_{1.0}, and they are distinguished from asthma by having < 10% reversibility in bronchodilator test.

After a run-in period of two visits to the medical center the patients (1277 patients finished the trial) suitable for the treatment started their medication or alternatively were given placebo (half of the group) on their third visit. They were closely followed during the three year period by regular visits to the medical center approximately every 2-3 months. The glucocorticosteroid was administered by inhalation of a dry powder formulation by using a Turbuhaler® breath-actuated dry-powder inhaler (budesonide, 400 µg twice a day). An equivalent placebo was used.

The FEV_{1.0} value of each patient was measured at each visit and the change in the value was noted. The results are presented in Figures 1 - 4. When presenting the results as change in FEV_{1.0} the slope of FEV_{1.0} for each patient was calculated by using a linear mixed effect model and thereafter mean slopes have been formed as shown in the figures. Each patient has been standardized to one starting value in order to be able to make a meaningful comparison of the progression of the disease against placebo values during the study period. Figure 1 represents all patients taken together and in Figures 2 - 4 the patients have been split up according to their smoking exposure. All values are mean values. One pack-year is defined as a smoker of 20 cigarettes per day for a year. Figure 2 shows the clear effect on patients having a smoking exposure of less than 26 pack-years, where the disease has not progressed as much as for the more heavy smokers (Figure 3 for less than 36 years and Figure 4 for more than 36 years). The results have also been summarized in Figure 5 showing the patients with < 26 pack-years having a smaller decline in FEV_{1.0} compared to the individuals with a higher and/or longer cigarette exposure.

CLAIMS

1. Use of a glucocorticosteroid for the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD) in patients having a FEV_{1.0} value > 65 %
5 of predicted value and < 10 % reversibility in bronchodilator test.
2. Use according to claim 1 for treatment during a period of at least one year.
3. Use according to claim 2 for treatment during a period of at least three years.
10
4. Use according to claim 1, wherein the glucocorticosteroid is budesonide or an isomer or an ester thereof.
5. Use according to claim 1, wherein the glucocorticosteroid is rofleponide or an ester
15 thereof.
6. Use according to any of the preceding claims, wherein the glucocorticosteroid is mixed with one or more pharmaceutically acceptable additives, diluents or carriers.
- 20 7. Use according to claim 6, wherein the glucocorticosteroid is mixed with one or more pharmaceutically acceptable additives, diluents or carriers in an amount of from 100 µg to 25 mg per dose.
8. Use according to claim 7, wherein the glucocorticosteroid is mixed with one or
25 more pharmaceutically acceptable additives, diluents or carriers in an amount of from 100 µg to 2000 µg per dose.
9. Use according to any one of claims 1-8, wherein the glucocorticosteroid is administered in the form of agglomerated steroid particles with a particle size of less than
30 10 µm.

10. Use according to any one of claims 1-8, wherein the glucocorticosteroid is administered in the form of agglomerated particles comprising the steroid and a carrier, both of which have a particle size of less than 10 μm .

5

11. Use according to any one of claims 1-8, wherein the glucocorticosteroid is administered in the form of an ordered mixture comprising steroid particles of a size less than 10 μm and coarser particles of a carrier.

10

12. Use according to any previous claim, wherein the amount of glucocorticosteroid administered to the patient lies in the range of from 100 μg to 3000 μg per day administered as a single or divided dose(s) one to four times per day.

15

13. Use according to claim 12, wherein the amount of glucocorticosteroid administered to the patient lies in the range of from 200 μg to 1600 μg per day.

14. Use according to claim 12 or 13, wherein the amount of glucocorticosteroid administered to the patient is 200 μg given twice a day or 400 μg given twice a day.

20

15. Use according to any one of claims 1-14, wherein the patients have a smoking exposure of less than 36 pack-years, suitably less than 26 pack-years, preferably less than 16 pack-years.

25

16. A method for treatment of chronic obstructive pulmonary disease (COPD) in patients having a $\text{FEV}_{1.0}$ value > 65 % of predicted value and < 10 % reversibility in bronchodilator test, wherein a therapeutically effective amount of a glucocorticosteroid is administered to a patient in need of such treatment.

17. The method according to claim 16 for treatment during a period of at least one year.

30

18. The method according to claim 17 for treatment during a period of at least three years.
19. The method according to any one of claims 16-18, wherein the glucocorticosteroid
5 is budesonide or an isomer or an ester thereof.
20. The method according to any one of claims 16-18, wherein the glucocorticosteroid is rofleponide or an ester thereof.
- 10 21. The method according to any one of claims 16-20, wherein the glucocorticosteroid is mixed with one or more pharmaceutically acceptable additives, diluents or carriers.
22. The method according to any one of claims 16-21, wherein the glucocorticosteroid is mixed with one or more pharmaceutically acceptable additives, diluents or carriers in an
15 amount of from 100 μ g to 25 mg per dose.
23. The method according to claim 22, wherein the glucocorticosteroid is mixed with one or more pharmaceutically acceptable additives, diluents or carriers in an amount of from 100 μ g to 2000 μ g.
20
24. The method according to any one of claims 16-23, wherein the glucocorticosteroid is administered in the form of agglomerated steroid particles with a particle size of less than 10 μ m.
- 25 25. The method according to any one of claims 16-23, wherein the glucocorticosteroid is administered in the form of agglomerated particles comprising the steroid and a carrier, both of which have a particle size of less than 10 μ m.

26. The method according to any one of claims 16-23, wherein the glucocorticosteroid is administered in the form of an ordered mixture comprising steroid particles of a size less than 10 μm and coarser particles of a carrier.

5 27. The method according to any one of claims 16-26, wherein the amount of glucocorticosteroid administered to the patient lies in the range of from 100 μg to 3000 μg per day administered as a single or divided dose(s) one to four times per day.

28. The method according to claim 27, wherein the amount of glucocorticosteroid
10 administered to the patient lies in the range of from 200 μg to 1600 μg per day.

29. The method according to claim 27 or 28, wherein the amount of glucocorticosteroid administered to the patient is 200 μg given twice a day or 400 μg given twice a day.

15 30. The method according to any one of claims 16-28, wherein the patients have a smoking exposure of less than 36 pack-years, suitably less than 26 pack-years, preferably less than 16 pack-years.

1 / 3
Fig. 1

Linear Change Over Time
All Patients

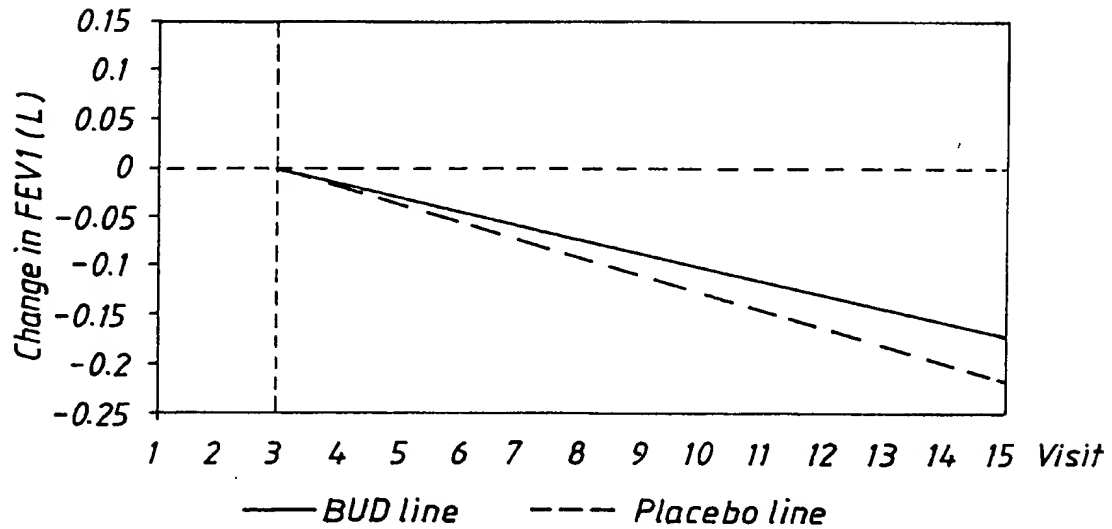
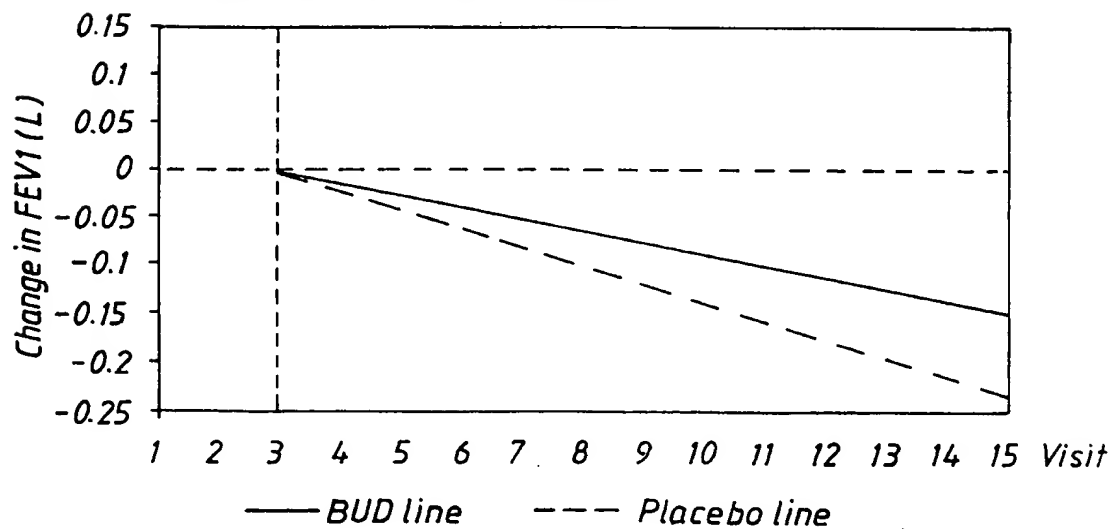


Fig. 2

Linear Change Over Time
Patients With <26 Pack years



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Fig. 3

Linear Change Over Time
Patients With < 36 Packyears

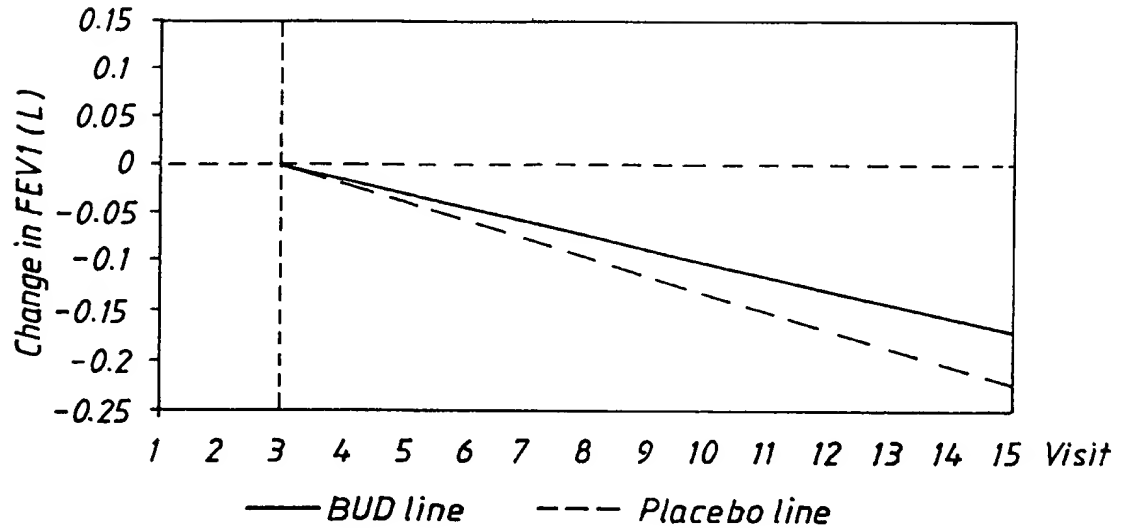
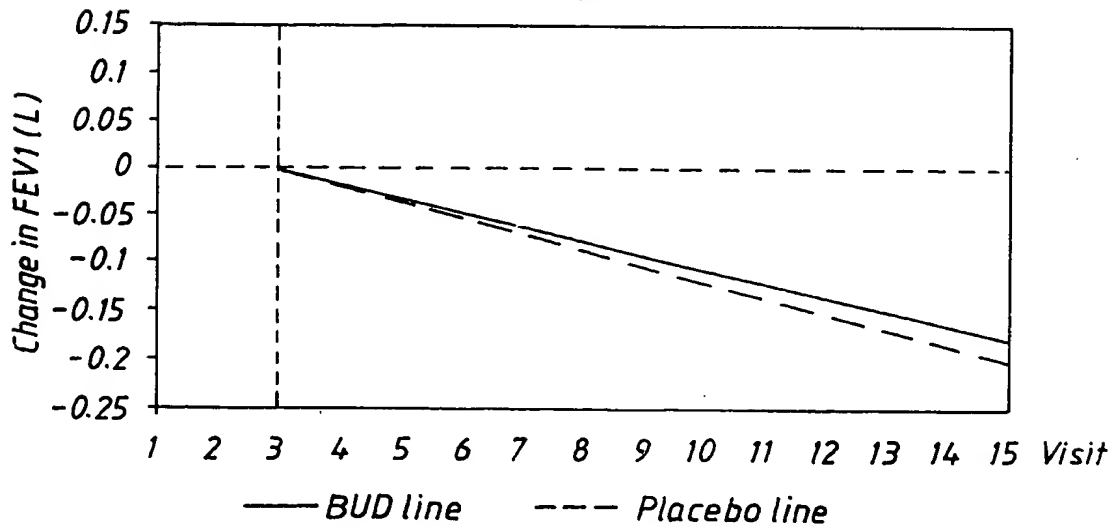


Fig. 4

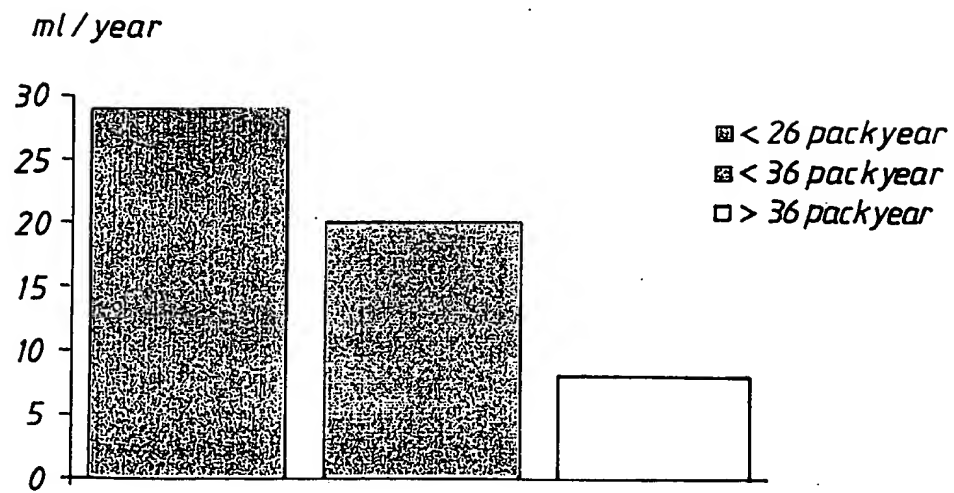
Linear Change Over Time
Patients With > 36 Packyears



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Fig. 5

*Difference in Linear Change Over Time
(Budesonide - Placebo), by Packyear*



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00426

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, EPODOC, WPI, JAPIO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chest., Volume 109, No 5, 1996, Tineke E.J. et al, "Effects of Long-term Treatment With Corticosteroids in COPD", page 1156 - page 1162, see page 1156, lines 21-23 --	1-30
A	Ohio state medical journal, Volume 70, No 7, 1974, Michael S. Kreindler, M.D. et al, "Allergic Bronchopulmonary Aspergillosis. An Unusual Clinical Presentation" page 421 - page 424 -- -----	1-30

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/SE99/00426**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **16-30**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00426

Claims 16-30 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.